MAYO CLINIC

MAYO CLINIC PROCEEDINGS:
INNOVATIONS, QUALITY & OUTCOMES

CASE REPORT

Implications of a Supernumerary Nipple Breast Cancer in a BReast CAncer Sequence Variation Carrier: A Case Report

Will Sperduto, MD, MBS; Ann McCullough, MD; Donald Northfelt, MD; Lisa McGee, MD; Barbara Pockaj, MD; and Kristen Jogerst, MD, MPH

Abstract

Supernumerary nipples develop on the chest and abdominopelvic regions along the embryonic milk line. Their anatomy varies from isolated accessory nipples to complete supernumerary nipples (accessory nipple, areola, and underlying glandular breast tissue). Patients with a pathogenic BReast CAncer (BRCA) sequence variation are at an increased cumulative risk of developing breast cancer, and it is the standard of care for them to be offered medical or surgical risk reduction. Given the relatively low prevalence of breast cancer within supernumerary nipples and ectopic glandular breast tissue, no current recommendations exist to guide multidisciplinary management of patients with BRCA sequence variations and ectopic breast tissue. Our case is of a 62-year-old female BRCA-1 carrier with a previous history of right breast cancer who developed a new primary breast cancer within a supernumerary nipple after undergoing surgical risk reduction. With no current consensus on the surgical management of supernumerary nipples in BRCA-1 carriers, our recommendation is to perform a thorough physical examination before risk-reducing operation. If supernumerary nipples or ectopic glandular breast tissue are present, wide-local excision of the tissue should be offered for more complete surgical risk reduction.

 ■ Mayo Clin Proc Inn Qual Out 2023;7(5):437-442

During the fourth week of embryological development, breasts begin to form in the pectoral region along the mammary ridge (milk line), which normally involutes during the fifth week.[1] Failure of the mammary ridge to regress leads to supernumerary nipples—accessory nipples that typically develop on the chest and abdominopelvic region along the embryonic milk lines. Their anatomy varies from isolated to complete supernumerary nipples comprising an accessory nipple, areola, and underlying glandular breast tissue. The prevalence of supernumerary nipples ranges from 1% to 5%; they are more frequently found in men, and they are rarely associated with an underlying ectopic breast cancer.[2] Of all breast cancers, 0.3% to 0.6% occur in ectopic breast tissue[3] and 5% of those cases are within supernumerary nipples.[4] Given their relative rarity, limited literature exists to guide the management of cancer in accessory breast tissue or supernumerary nipples. Germline BRCA sequence variation prevalence in triple-negative breast cancer patients has been reported as high as 36.9%.[5] Given the cumulative risk of developing breast cancer by the age of 70 years is 60% for BRCA-1 carriers and 55% for BRCA-2 carriers, current National Comprehensive Cancer Network guidelines include surgical risk reduction with prophylactic bilateral mastectomy.[6,7] Although 1 case report describes prophylactic resection of supernumerary nipple accessory gland tissue in a BRCA-2 (+) man,[8] none have shown negative sequelae if supernumerary nipple resection is not completed at the time of surgical risk reduction. Despite a prevalence of supernumerary nipples and BRCA germline sequence variations as high as 5% and 36%, respectively, there have been limited discussions about the potential benefit of complete surgical risk reduction in BRCA-1 carriers who have supernumerary nipples. The current report aims to (1) raise awareness of supernumerary nipple appearance and typical

Department of Radiation Oncology (W.S., L.McG.), Department of Pathology (A.McC.), Department of Medicine, Division of Hematology and Medical Oncology (D.N.), and Department of Surgery (B.P., K.J.), Mayo Clinic, Phoenix, AZ; and Department of Surgery, Massachusetts General Hospital, Boston, (K.J.).

locations; (2) describe the presentation and management of a patient with new primary triple-negative breast cancer within a supernumerary nipple years after a risk-reducing operation for her BRCA-1 sequence variation; (3) reinforce the importance of a careful physical examination; and (4) advocate for similar surveillance and treatment guidelines for ectopic and pectoral breast tissue.

CASE REPORT

A 62-year-old woman presented to the surgical oncology clinic with a 1-month history of a new left chest wall mass. Her oncologic history began in June 2002, when she noticed a palpable right breast mass. An outside hospital image-guided biopsy revealed a grade 3 invasive ductal carcinoma (IDC), estrogen receptor (ER)-positive, progesterone receptor (PR)-negative, and human epidermal growth factor 2 (HER2) hormone receptor percentages not reported (0). Preoperatively, she did not have clinically palpable right axillary lymph nodes, suspicious lymph nodes on imaging, or evidence of metastasis. After shared decision-making, the patient underwent a total mastectomy and sentinel lymph node biopsy. The sentinel lymph node biopsy was positive for metastatic disease at frozen section, and a complete lymph node dissection was performed at the time of operation. Final pathology revealed a 3.9 × 2.8 × 1.9 cm grade 3 IDC, ER negative, PR negative, and HER2 negative (0); final disease stage was pT2pN1cM0. After operation, she received 3 of the 4 planned cycles of adjuvant doxorubicin and cyclophosphamide chemotherapy; the fourth cycle was cancelled because of neutropenia. This was followed by 12 weeks of weekly adjuvant paclitaxel. She then completed adjuvant external beam radiotherapy to the right chest wall and regional lymphatics, including the intramammary nodal area, consisting of 50.4 Gy in 28 fractions with a chest wall boost for a total dose of 60.4 Gy delivered over 33 fractions. She then began 5 years of adjuvant tamoxifen therapy.

In October 2004, she noticed a right chest wall mass. Image-guided biopsy confirmed a 3.6 cm grade 3 IDC, ER positive (1%-10%), PR negative (0%), and HER2 negative (0) local recurrence within the prior radiation field. In November 2004, she underwent wide-local excision of this mass, including pectoralis minor resection, and achieved malignancy-free margins. Postoperatively, she completed 4 cycles of adjuvant paclitaxel and carboplatin chemotherapy. At this time, she was postmenopausal and initiated adjuvant aromatase inhibitor therapy.

In February 2012, the patient's sister was diagnosed with breast cancer, and genetic testing discovered her sister had a BRCA-1 sequence variation. Given this family history and her personal history of breast cancer, the patient was screened for germline sequence variations and found to be a BRCA-1 carrier. After genetic and surgical counseling, the patient underwent risk-reducing contralateral mastectomy, hysterectomy, and bilateral salpingo-oophorectomy. She discontinued exemestane in June 2012 and continued annual observation with medical oncology visits through November 2017.

She returned to the surgical oncology clinic in January 2018 with a 1-month history of a new left chest wall mass. Ultrasound-guided biopsy was consistent with a grade 3 IDC, ER negative (0%), PR negative (0%), and HER2 negative (0) new primary cancer. Given concern for the mass potentially arising from residual breast tissue after the previous left prophylactic mastectomy, a thorough physical examination was performed. The mass was inferior to the left mastectomy site and deep to a supernumerary nipple. Further physical examination revealed 3 other

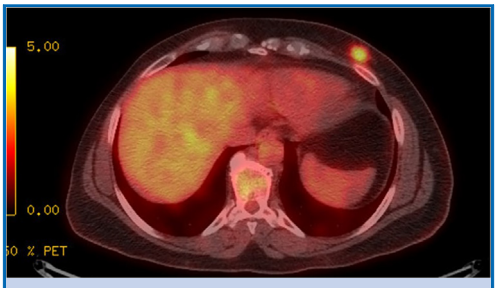

FIGURE 1. Positron emission tomography—computed tomography (PET-CT) preoperative imaging reports a hypermetabolic left anterior chest wall subcutaneous nodule, consistent with the biopsy-proven malignancy. Imaging obtained on February 7, 2018.

Mayo Clin Proc Inn Qual Out ■ October 2023;7(5):437-442 ■ https://doi.org/10.1016/j.mayocpiqo.2023.08.006
www.mcpiqojournal.org

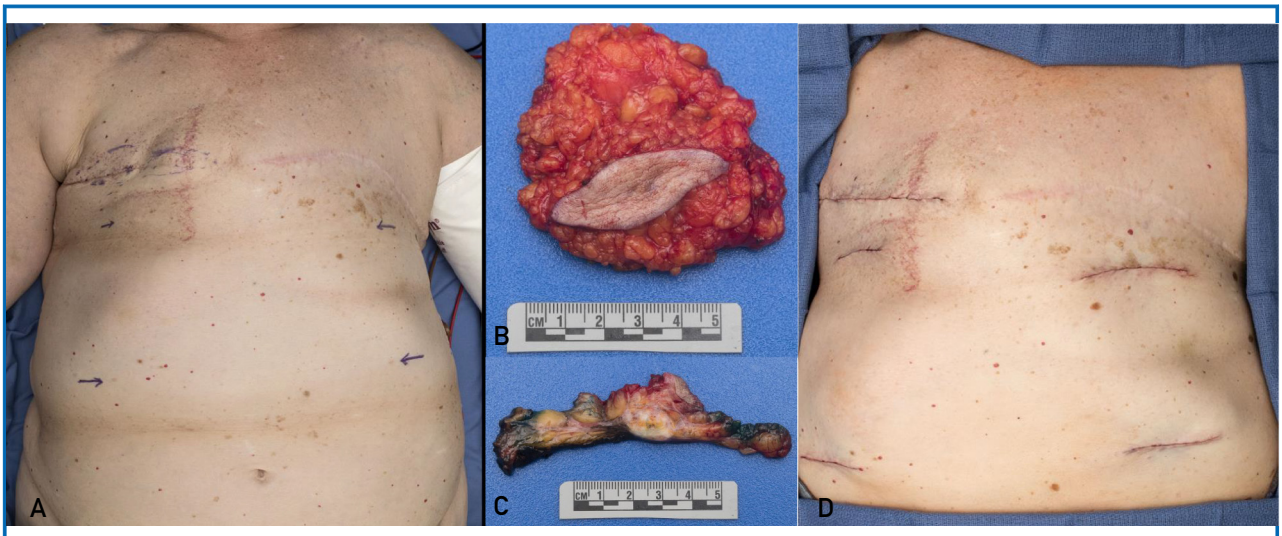

FIGURE 2. Surgical images (A) Preoperative site marking with blue arrows pointing to supernumerary nipples. Patient had also asked for right mastectomy scar revision and the excess scar is also outlined with blue surgical marking. (B) Left chest wall supernumerary breast cancer specimen sent for final pathology. (C) Cross-section of the left chest wall supernumerary breast cancer specimen showing the tumor measuring approximately 2cm in maximal dimension. (D) Final surgical result showing the wide-local excisions of supernumerary breast tissue × 4, along with right mastectomy scar revision. Images obtained on February 9, 2018.

supernumerary nipples along the milk lines without underlying palpable masses.

Staging positron emission tomography (PET)-computed tomography (CT) found no evidence of metastatic disease (Figure 1). In February 2018, the patient underwent wide-local excisions of her 3 supernumerary nipples and the left lower chest wall breast cancer (Figure 2). Surgical margins were free of malignancy, and final pathology revealed a 1.8 cm grade 3 IDC, ER negative (0%), PR negative (0%), and HER2 negative (0) at the

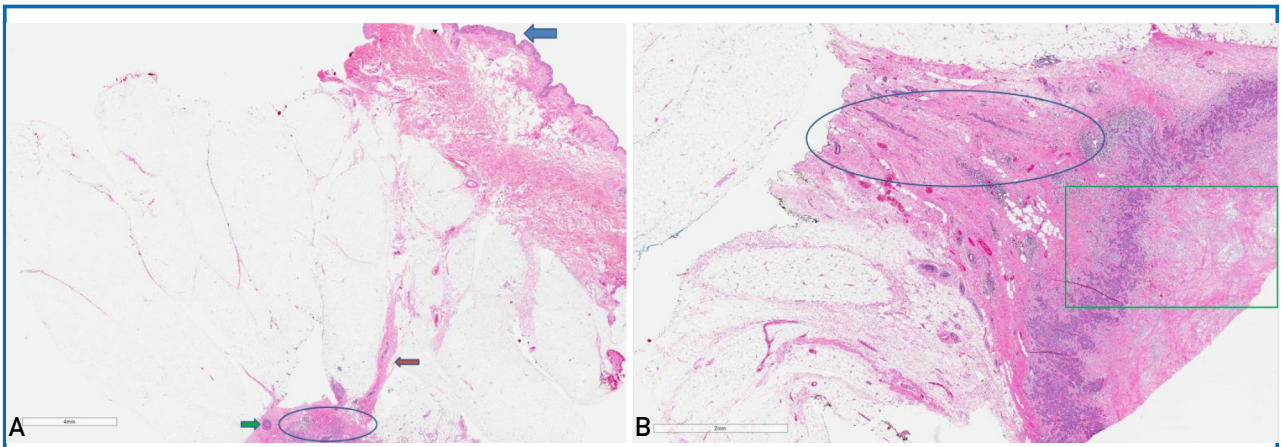

FIGURE 3. Pathology whole mount sections, Hematoxylin & Eosin, 2× and 4×. (A) Blue arrow is a keratotic skin lesion. Red arrow is a fibrous tract with benign accessory nipple ducts. Green arrow is a focus of ductal carcinoma in situ. Blue oval surrounds invasive carcinoma. (B) Blue oval shows a fibrous tract with benign accessory nipple ducts deep to the carcinoma. Green rectangle shows an invasive carcinoma with central sclerosis growing in the tract of the accessory nipple. Images obtained on February 9, 2018.

left lower chest wall, consistent with her preoperative biopsy results (Figure 3). The patient did well and had no postoperative complications. She then completed adjuvant chemotherapy (6 cycles of carboplatin and olaparib)[9] and adjuvant radiotherapy (40.05 Gy over 15 fractions) to the left chest wall and axillary lymph node levels I and II. From August 2018 through March 2023, she was monitored every 6 months, remained without evidence of recurrence, and had no surgical or adjuvant treatment complications. Currently, the patient has surpassed the 5-year disease-free survival milestone and transitioned to annual follow-up visits.

DISCUSSION

To our knowledge, this is the first case of a patient with a BRCA sequence variation presenting with primary breast cancer in a supernumerary nipple, despite previous surgical risk reduction. Fortunately, wide-local excision of her new primary breast cancer along with adjuvant platinum-based and poly (adenosine diphosphate—ribose) polymerase inhibitor chemotherapy, adjuvant radiotherapy, and frequent surveillance helped this patient achieve a 5-year disease-free survival. However, during her initial surgical risk reduction, her 4 supernumerary nipples and associated ectopic breast tissue, and thus an opportunity for oncologic prevention, were missed. A growing number of case reports and series describe ectopic breast cancer occurring in both men and women along the embryonic milk lines. Most often, they occur in the axilla[10-12] or along the chest wall,[13] and less often on the perineum[14] or vulva.[15,16] Although less than 1% of breast cancers occur in supernumerary nipples, none have been described in BRCA carriers. Given the high prevalence of BRCA sequence variations, particularly in patients with triple-negative breast cancer, it is likely that other unreported cases have previously occurred or could occur. Previous literature regarding management of breast cancer in supernumerary nipples demands prudent physical examination to avoid misdiagnosis or delayed detection.

The reported prevalence of supernumerary nipples ranges from 1% to 5%.[2,17] The reported prevalence of BRCA germline sequence variations in female patients ranges from 1.8% in those with sporadic breast cancer to 37% in those with triple-negative disease. Unfortunately, the prevalence of supernumerary nipples in patients with BRCA sequence variations is poorly understood, as most literature describing breast cancer in ectopic tissue is limited to case reports. In patients carrying BRCA-1 sequence variation(s), the cumulative risk of developing breast or ovarian cancer up until the age of 80 years is 72% and 44%, respectively.[18] For female BRCA-1/2 sequence variations, prophylactic mastectomies and salpingo-oophorectomies are offered and can provide a 90% to 95% risk reduction in breast and ovarian cancer.[6,19] At the time of risk reduction counseling, a prudent physical examination is necessary to identify any potential ectopic breast tissue. Once identified, the approach to surgical risk reduction should follow the same principles as the management of orthotopic breast tissue, with the goal of removing all the breast tissue. If diagnosed with breast cancer, tumor, nodal, and metastatic staging and treatment are similar for ectopic and orthotopic tissue.[4,20,21] Should a patient not want prophylactic resection of their accessory breast tissue, our recommendation would be to treat the ectopic breast tissue like pectoral breast tissue and undergo the same high-risk screening recommended for BRCA carriers. Depending on the location of the ectopic tissue, this anatomic region would need to be included in the magnetic resonance imaging or ultrasound imaging field.[6]

For patients with new ectopic breast malignancies, sentinel lymph node biopsy should be employed, and preoperative lymphoscintigram may be useful. Given a negative preoperative clinical lymph node examination and PET-CT and possible disruption of normal breast lymphatic drainage during her left prophylactic mastectomy, the surgical team felt this patient was at low risk for axillary lymph node metastases, and a sentinel lymph node biopsy was not performed. Instead, she completed adjuvant radiotherapy (40.05 Gy over 15 fractions) to the left chest wall supernumerary breast cancer site and the axillary lymph node levels I and II.[22] She had no evidence of disease recurrence or arm morbidity at her most recent follow-up in March 2023. The management of ectopic breast malignancies with adjuvant chemotherapy,

Mayo Clin Proc Inn Qual Out ■ October 2023;7(5):437-442 ■ https://doi.org/10.1016/j.mayocpiqo.2023.08.006
www.mcpiqojournal.org

aromatase inhibitors, or targeted agents follows the biological principles for management of orthotopic breast cancers. This case was in a patient with a BRCA-1 pathologic sequence variation, so she underwent poly (adenosine diphospahte–ribose) polymerase inhibitor and platinum-based chemotherapy for her triple-negative hormone receptor tumor biology.

Currently, the National Comprehensive Cancer Network only offers surveillance and management guidelines for pectoral breast cancer. Given a lack of awareness about supernumerary nipples, their potential for malignant development, and their atypical presentation, patients with ectopic breast malignancies often present with more advanced disease and have worse overall outcomes.[12,23] Increased awareness is needed to achieve earlier detection and treatment and improve patient outcomes. Across similar stages and histologies, pectoral and ectopic breast cancer tend to have similar outcomes.[24] Should primary care physicians recognize accessory nipples on physical examination, this should be documented. In addition, this tissue should be treated like pectoral breast tissue and included in a patient's annual breast cancer screening. Should the patient undergo genetic screening and have BRCA-1 or BRCA-2 sequence variations, surgeons should follow the surgical risk-reduction treatment principles used for the management of pectoral breast tissue and offer patients prophylactic wide-local excision of their ectopic breast tissue. Finally, all new cases of ectopic breast tissue malignancy should be documented in a national registry to aid in the development of consensus guidelines for multidisciplinary management.[10]

CONCLUSION

This case reports that patients with supernumerary nipples and BRCA sequence variations can develop new primary malignancies in ectopic breast tissue. It also emphasizes the importance of a thorough preoperative physical examination when counseling for surgical risk reduction. Given that all breast tissue is at risk for development of breast cancer in patients with inheritable BRCA sequence variation(s), if patients have ectopic glandular breast tissue, they should be offered wide-local excision of this tissue for more complete surgical risk reduction.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

Abbreviations and Acronyms: **BRCA 1,** BReast CAncer 1; **BRCA 2,** BReast CAncer 2; **ER,** estrogen receptor; **Gy,** Gray; **HER2,** human epidermal growth factor receptor 2; **IDC,** invasive ductal carcinoma; **PET-CT,** positron emission tomography–computed tomography; **PR,** progesterone receptor

Correspondence: Address to Kristen Jogerst, MD, MPH, 55 Fruit Street, GRB-425, Boston, MA 02114 (KJOGERST@mgh.harvard.edu).

REFERENCES

1. Velanovich V. Ectopic breast tissue, supernumerary breasts, and supernumerary nipples. *South Med J*. 1995;88(9):903-906.
2. Schmidt H. Supernumerary nipples: prevalence, size, sex and side predilection—a prospective clinical study. *Eur J Pediatr*. 1998;157(10):821-823.
3. Famá F, Cicciú M, Sindoni A, et al. Prevalence of ectopic breast tissue and tumor: a 20-year single center experience. *Clin Breast Cancer*. 2016;16(4):e107-e112.
4. Marshall MB, Moynihan JJ, Frost A, Evans SR. Ectopic breast cancer: case report and literature review. *Surg Oncol*. 1994; 3(5):295-304.
5. Armstrong N, Ryder S, Forbes C, Ross J, Quek RG. A systematic review of the international prevalence of BRCA mutation in breast cancer. *Clin Epidemiol*. 2019;11:543-561.
6. Daly MB, Pal T, Berry MP, et al. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2021;19(1):77-102.
7. Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst*. 2013;105(11):812-822.
8. McKay M, Coad R. A brother and sister with breast cancer, BRCA2 mutations and bilateral supernumerary nipples. *Ann Transl Med*. 2017;5(5):106.
9. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. *N Engl J Med*. 2021;384(25):2394-2405.
10. Addae JK, Genuit T, Colletta J, Schilling K. Case of second primary breast cancer in ectopic breast tissue and review of the literature. *BMJ Case Rep*. 2021;14(4):e241361.
11. Conversi A, Meggiorini ML, Fino P, Soda G, Scuderi N, Onesti MG. Axillary ectopic lobular carcinoma of breast: two rare case reports. *Eur Rev Med Pharmacol Sci*. 2017;21(18): 4124-4128.
12. Zhang S, Yu YH, Qu W, Zhang Y, Li J. Diagnosis and treatment of accessory breast cancer in 11 patients. *Oncol Lett*. 2015; 10(3):1783-1788.
13. Page BR, Ahmed F, Thomson JW. Definitive treatment of supernumerary lower chest wall primary breast cancer. *Pract Radiat Oncol*. 2012;2(4):e53-e57.
14. Eom HJ, Ko BS, Song IH, Gong G, Kim HH. Ectopic male breast cancer in the perineum: a case report. *J Breast Cancer*. 2017; 20(4):404-407.
15. Guerry RL, Pratt-Thomas HR. Carcinoma of supernumerary breast of vulva with bilateral mammary cancer. *Cancer*. 1976; 38(6):2570-2574.

16. Hendrix RC, Behrman SJ. Adenocarcinoma arising in a supernumerary mammary gland in the vulva. *Obstet Gynecol*. 1956;8(2):238-241.
17. Pandya S, Moore RG. Breast development and anatomy. *Clin Obstet Gynecol*. 2011;54(1):91-95.
18. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA*. 2017;317(23):2402-2416.
19. Conte C, Pelligra S, Sarpietro G, et al. Hereditary women's cancer: management and risk-reducing surgery. *Medicina (Kaunas)*. 2023;59(2):300.
20. Francone E, Nathan MJ, Murelli F, Bruno MS, Traverso E, Friedman D. Ectopic breast cancer: case report and review of the literature. *Aesthetic Plast Surg*. 2013;37(4):746-749.
21. Botty Van den Bruele A, Gemignani ML. Management of ipsilateral supernumerary nipple at time of breast cancer diagnosis. *Breast J*. 2020;26(10):2042-2044.
22. Bartels SAL, Donker M, Poncet C, et al. Radiotherapy or Surgery of the axilla after a positive sentinel node in breast cancer: 10-year results of the randomized controlled EORTC 10981-22023 AMAROS trial. *J Clin Oncol*. 2023;41(12):2159-2165.
23. Munrós J, Vázquez M, Santiago P, Romay G, Acea B. Management of breast carcinoma in ectopic axillary breast tissue. *Cir Esp*. 2017;95(4):232-233.
24. Devine C, Courtney CA, Deb R, Agrawal A. Invasive lobular carcinoma arising in accessory breast tissue. *World J Surg Oncol*. 2013;11:47.

Mayo Clin Proc Inn Qual Out ■ October 2023;7(5):437-442 ■ https://doi.org/10.1016/j.mayocpiqo.2023.08.006
www.mcpiqojournal.org